REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1-25 are pending with entry of this amendment, claims 8-25 being withdrawn from consideration pursuant to a restriction requirement. Claims 1, 4 and 8 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claim 1, support for an IPG synthetic analogue which has the ability to activate pyruvate dehydrogenase phosphatase is found, e.g., on page 11, , line 24, on page 12, lines 23-24, and in figure 6, as originally filed.

The amendment to claim 4 has been made solely to clarify that "thereof" refers to adenine nucleotide synthesis, as is implicit in the claim as originally filed.

The amendment to claim 8 has been made solely to clarify that regardless of whether IPG or an IPG synthetic analogue is present in the composition, ribose is also present, i.e., in a pharmaceutically acceptable excipient.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Election/Restriction Requirement.

Pursuant to a restriction requirement, Applicants acknowledge the withdrawal of claims 8-25. Applicants maintain that claims 1-7 and 8-25 share a special technical feature, and, thus relate to the same inventive concept. Accordingly, in the event that claims of group I are found patentable, Applicants reserve the right to have the remaining claims rejoined.

The Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449) submitted on February 27, 2002.

Specification

The specification was objected to as failing to provide proper antecedent basis for claim 7 directed to a composition in powder or concentrate form that can be used to prepare a liquid composition, on the grounds that the specification does not teach "that the powder of concentrate form can be used to prepare a liquid composition.

As a preliminary matter, Applicants infer that the Office Action refers to claim 6 rather than claim 7. The specification at page 7, line 31 to page 8, line 2 states: "the composition is supplied as a powder or concentrate from which a liquid composition can be

prepared." Accordingly, the specification provides explicit and literal, i.e., verbatim support for the subject matter of claim 6, and the objection should be withrdrawn.

35 U.S.C. §112, First Paragraph.

Claims 1 and 4-7 under 35 U.S.C. § 112, paragraph 1 for lack of enablement. The Office Action alleges that undue experimentation would be required by one of skill in the art to make and use compositions comprising IPG type A. However, the Examiner finds that the specification is enabling for P-type IPGs. In particular, the Examiner cites Caro et al. (Biochemical and Molecular Medicine, **1997** 61:214-228) as evidence that A-type IPGs are not known to stimulate PDH phosphatase.

Although this paper describes PDH-phosphatase activation as an activity primarily of P-type IPGs, it also discloses (page 222, col. 2) that type A IPGs also stimulate the enzyme, i.e., to an extent 2.8 fold less than type P. Therefore, A-type IPGs give the desired stimulation of PDH phosphatase. Furthermore, by defining the comparative level of stimulation, Caro gives the skilled person a concrete suggestion of how much A type IPG would be necessary to get an effect similar to a given amount of P type IPG. Accordingly, the specification is enabling for enabling for A-type IPGs, as well as P-type IPGs, and the rejection should be withdrawn.

35 U.S.C. §112, Second Paragraph.

Claims 1 and 3-7 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the properties of the claimed "IPG synthetic analogue" and the term "nucleotide precursor" are indefinite.

Claim 1 is amended herein to define the term "IPG synthetic analogue" as an analogue having the ability to activate pyruvate dehydrogenase phosphatase. Support for this amendment is found at page 11, line 24, page 12, lines 23-24 and figure 6. Additionally, it is clear from the description that an analogue with the claimed function will achieve the aim of the present invention, i.e. will increase the energy generating systems of the cell and protect against anoxia (see page 16, line 30 – page 17, line 15). This definition of "IPG synthetic analogue" enables the skilled person to determine whether a given compound falls within the claims. The ability to activate PDH phosphatase is a parameter measurable by techniques well known to those of skill in the art (and described in the application). Accordingly, it would be a simple and straightforward matter to test whether any particular IPG analogue falls within the metes and bounds of the claim.

The term "nucleotide precursor thereof" in claim 4 has been amended to "precursor of adenine nucleotide synthesis." Support for this amendment is found at page 17, lines 29 to 30. The skilled person will be well aware of the various reactions which take place in the biosynthesis of adenine nucleotides, and the appropriate substrates for those reactions. Therefore, the meaning of this term is clear-it refers to any compound which can serve as a substrate in one or more reactions in biosynthesis of adenine nucleotides. The skilled person can therefore readily determine whether or not a given composition falls within the scope of the claim.

35 U.S.C. §103(a).

Claims 1-7 were rejected under 35 U.S.C. §103(a) as allegedly obvious over a combination of Zimmer et al. (Molecular and Cellular Biochemistry, **1996** 160/161:101-109; Stanley et al. Cardiovascular Research, **1997** 33:243-257 and PCT publication WO 98/11435 to Hoeft Rademacher Ltd.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims. M.P.E.P § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. In re Geiger, 815 USPQ2s 1276, 1278 (Fed. Cir. 1987). Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991), citing In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion to combine and the expectation of success must be found in the prior art, and not based on Applicants' disclosure. M.P.E.P. §2143.

The Office Action alleges that Zimmer teaches 1) that ribose can be used to increase the level of PRPP in the heart; and 2) suggests the use of ribose in conjunction with other therapeutic agents. The Examiner admits that Zimmer does not teach the use of any compound that activates PDH via stimulation of PDH phosphatase, or the combination of such a compound with ribose. Nor does Zimmer disclose either treatment with an IPG or IPG in combination with ribose.

The Office Action also alleges that Stanley teaches that one potential method of treating heart disease is by directly activating PDH. The Examiner further alleges that because WO 98/ 11435 is teaches that IPG P-type activates pyruvate dehydrogenase phosphatase, and can be employed as a therapeutic agent for the treatment of diabetes, it would be obvious to combine ribose with IPGs as a treatment for ischaemia to achieve the invention of claims 1-7. Applicants traverse.

Firstly, we would like to point out that this is a mosaic of the teaching of three documents which is clearly based on *ex post facto* analysis of the present invention. As a preliminary matter, the cited references do not provide a "composition comprising an inositolphosphoglycan (IPG) or an IPG synthetic analogue and ribose..." The cited art provides no incentive to use ribose in conjunction with any particular drugs for therapy of heart disease other than those listed in Zimmer, i.e., verapamil (a calcium blocker), metoprolol (a β-blocker), adenine and inosine (ATP salvage pathway precursors). The Examiner admits that Zimmer does not discuss stimulators of mitochondrial oxidative phosphorylation in general, or IPGs in particular. Indeed, Zimmer neither mentions such compounds, nor suggests the combination of such compounds with ribose can be used as therapies for the treatment of ischaemia. Nor does anything in Stanley or in PCT publication WO 98/11435 (which relates to the use of IPGs in the treatment of diabetes) suggest that the combination of ribose and an IPG or IPG analogue would be useful for the treatment of ischaemia, and the rejection should be withdrawn.

Futhermore, the Examiner's argument presupposes that the present invention is a simple collocation of two unrelated therapeutics which provide no unexpected benefit when used together. This is not the case. The present inventors have realized that the lack of ATP in ischaemic heart disease fundamentally limits the therapeutic benefit that administration of ribose can provide. This is because the biosynthetic pathways which are fed by ribose (the de novo and salvage pathways) are themselves dependent on ATP (*see*,

e.g., page 3, lines 14 to 23 of the present application). Therefore coadministration of a suitable stimulator of mitochondrial oxidative phosphorylation, namely IPG, actually increases the benefit from administration of ribose by providing two distinct means of replenishing the energy charge of the cell, and so increasing the rate at which the biosynthetic pathways can operate.

The Examiner points to no teaching in the prior art either that such a problem exists with administration of ribose as a therapy, or that it could be solved by administration of ribose in combination with a stimulator of oxidative phosphorylation, still less in combination with IPG.

In addition, use of IPGs to activate PDH enables ATP to be synthesized following ischaemia without production of lactic acid. This is explained in the application at page 16, lines 23 to 28. This is a significant difference from known formulations for treatment of ischaemia, because lactic acid is a by-product which contributes to reperfusion injury following ischaemia, particularly in stroke and post-ischaemic heart disease. This undesirable effect is avoided by the compositions and methods of the present invention.

Thus, as explained in the teachings of the present application, the present invention provides unexpectedly superior results with respect to the prior art, indicating that the invention is non-obvious.

Accordingly, Applicants respectfully submit that the present claims are non-obvious over the cited prior art.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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Respectfully submitted,

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Attachments:

1) A petition to extend the period of response for **three** months;
2) A transmittal sheet;
3) A fee transmittal sheet; and,
4) A receipt acknowledgement postcard.